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ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/830,451	SCHOFIELD ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 May 1807*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18 and 79-137* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,9-16,18,81-88,100,102-106,108-110,116-120,124 and 125* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/11/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 4-8,17,79,80,89-99,101,107,111-115,121-123 and 126-137.

DETAILED ACTION

1. Applicant's amendment filed 5/18/07 is acknowledged and has been entered.

The Declaration of Louis Schofield and Diana Hansen under 35 USC 1.132 filed 5/18/07 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election with traverse of Group I (claims 1-18 and 79-125), and species election of inducing an immune response, upregulation of the Th2 response, treatment or prophylaxis of the disease condition malaria using a GPI with the sequence EtN-P-[Mα2]Mα2Mα6Mα4Gα6Ino-Y in Applicant's response filed 10/17/03.

Claims 1-3, 9-16, 18, 81-88, 100, 102-106, 108-110, 116-120, 124 and 125 are presently being examined.

The following are new grounds of rejection necessitated by Applicant's amendment filed 5/18/07.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-3, 9-16, 18, 103-106, 108-110, 116-120, 124 and 125 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed method of activating CD1-restricted Th cells (including CD1+ NK1.1+ T cells, Th2 cells), said method comprising administration of a complex comprising GPI, including for treatment or prophylaxis via administration of a GPI complex.

The instant claims encompass use of a complex of GPI that comprises a molecule other than a protein or peptide antigen to activate or induce Th cells *in vitro* or *in vivo*, including for treatment or prophylaxis.

The specification discloses that GPIs consist of a conserved core glycan (Manα1-2Manα1-6Manα1-4GlcNH$_2$ linked to the 6 position of the myo-inositol ring of PI (sentence spanning pages 1 and 2). The specification further discloses other GPI that do not appear to comprise the conserved core glycan as defined above (pages 3-7), for example, EtN-P-Manα2-Manα6-M-Y (page 4 at line 2) or Manα2-Manα6-M-Y (page 7 at line 1). The specification discloses that "GPI complex" is a reference to a GPI moiety coupled to any other molecule, and said molecule may be any molecule for which an immune response is sought, for example, a carbohydrate or a peptide or protein (page 20 at lines 29-31).

The specification as filed does not provide written description support for any molecule in complex with "a GPI moiety" except for an antigenic peptide or protein. Adequate written description requires more than a mere statement that it is part of the invention and along with a recitation of a function such as inducing Th cells. The derivative or equivalent itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

In addition, a definition by function does not suffice to define the genus because it is only an indication of what the property the peptide has, and if one extends the analysis in the instant case, what the peptide does (*i.e.*, it induces a CD1-restricted Th cell response), rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06. It is only a definition of a useful result rather than a definition of what achieves that result. Many such species may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. One of ordinary skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

Applicant's arguments in the amendment filed 5/18/07 have been fully considered, but are not persuasive.

Applicant's position is of record on pages 15 and 16, briefly that: (1) Applicant has amended the independent claims to delete the reference to "derivative" or "equivalent" of GPI and to defined the structure of the GPI molecule by its conserved core glycan, and (2) Applicant has amended the dependent claims to delete those formulas that do not contain the conserved core glycan.

It is the Examiner's position that the instant specification has not provided written description for the claimed method of activating Th cells comprising administering a GPI complex, including for the treatment and/or prophylaxis of a mammalian disease condition, and including those conditions recited in the instant claims.

5. Claims 1-3, 9-16, 18, 103-106, 108-110, 116-120, 124 and 125 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed method of activating Th cells, inducing an immune response in a mammal directed to GPI, or treating malarial disease by administering GPI comprising the structure recited in the instant claims that binds to CD1 and activates NK1.1 CD4+ Th cells, or inducing an immune response in a mammal to a protein or peptide antigen linked to GPI, does not reasonably provide enablement for the claimed method of activating Th cells comprising administering a GPI complex wherein the antigen or non-GPI component of the said complex is not a peptide or protein antigen, inducing an immune response in a mammal directed to GPI comprising administering a GPI complex wherein the non-GPI component of the said complex is not a peptide or protein antigen, or prophylaxis of malarial disease or of any other disease condition by administering a GPI or a GPI complex. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The instant claims encompass activating Th cells or inducing an immune response, including for treatment and/or prophylaxis, including prevention, of any mammalian disease condition with GPI "complexes" that the specification does not disclose how to make, the non-GPI component in the GPI "complex" not necessarily a peptide or protein antigen, and prevention of any disease using GPI or GPI complexes.

The specification discloses that GPIs consist of a conserved core glycan (Manα1-2Manα1-6Manα1-4GlcNH$_2$ linked to the 6 position of the myo-inositol ring of PI (sentence spanning pages 1 and 2). The specification further discloses other GPI that do not appear to comprise the conserved core glycan as defined above (pages 3-7), for example, EtN-P-Manα2-Manα6-M-Y (page 4 at line 2) or Manα2-Manα6-M-Y (page 7 at line 1). The specification further that "GPI complex" is a reference to a GPI moiety coupled to any other molecule, and said molecule may be any molecule for which an immune response is sought, for example, a carbohydrate or a peptide or protein (page

20 at lines 29-31).

The disclosed use of the invention is to regulate the Th1/Th2 response in order to therapeutically or prophylactically treat disease conditions that show a pronounced Th1/Th2 dependence such as cerebral malaria, tuberculosis, leprosy, leishmaniasis, type I diabetes, autoimmune arthritis, SLE and erythromatosis, cancer, or others, and/or providing B cell help for antibody production by inducing a Th2 response (especially paragraph spanning pages 35-36).

The specification does not disclose any working examples of treatment or prophylaxis of any condition or disease *in vivo*, including in a mammal, comprising administration of GPI or GPI complexes, nor of prophylaxis of any disease using GPI or GPI complexes.

Evidentiary reference Carvalho *et al* (Scand. J. Immunol. 2002, 56: 327-343, of record) teach that an effective malaria vaccine is not yet available. Carvalho *et al* teach that an astonishing amount of data has accumulated concerning parasite biology, host-parasite interactions, immunity and escape mechanisms, targets and modulators of immune responses, but nevertheless, this knowledge has not been enough to make us understand how to properly manipulate the whole system to build an effective vaccine (especially abstract). Carvalho *et al* teach that the acquisition of immunity in malaria is still far from being a well-understood phenomenon, and that no reliable correlates of protection have been identified so far, turning malaria vaccine research into an essentially empirical or semi-empirical approach (especially paragraph spanning pages 329-330). Carvalho *et al* teach that murine malaria is quite different from human malaria, and the mechanisms of immunity acting in such models may have no relevance for humans (especially paragraph spanning columns 1-2 on page 330). Carvalho *et al* teach "In conclusion, we would like to stress that most of the data supporting the current vaccine candidate antigens rely on the three above approaches, *i.e.,* epidemiological associations between protection and antigen recognition by exposed individuals, antiparasitic effect *in vitro* and experiments in animal models. As their relevance is far from being well established and consensual, they mostly function as a guide rather than as a secure way for finding and studying potential candidate antigens. It means that many times the bet on a new antigen is a shot in the dark" (especially first full paragraph, column 2 on page 330).

Evidentiary reference Websters Online Dictionary (of record) teaches that prophylaxis is the prevention of disease, and that prophylaxis refers to any medical or public health procedure whose purpose is to prevent, rather than treat or cure, disease.

Evidentiary reference MedicineNet.com (of record) teaches that prophylaxis is a measure taken for the prevention of a disease or condition.

Undue experimentation would be required of one skilled in the art to practice the instant invention. See *In re Wands* 8 USPQ2d 1400 (CAFC 1988).

Applicant's arguments in the amendment filed 5/18/07 have been fully considered, but are not persuasive.

Applicant's position is of record on pages 15-19 of the said amendment, briefly, as regards the instant rejection that: (1) that the argument to treatment or prophylaxis should apply only, if at all, to claims 103, 109, 124 and their dependent claims, but not to claims 1, 18 and 81 or their dependent claims, (2) other references contradict the position of evidentiary reference de Souza *et al*, and that the latter discusses the protective role of antibodies against GPI, which discussion is irrelevant to the present invention which is directed to the activation of T cells, (3) GPIs have been shown to activate NK-T cells as in Schofield *et al*, (4) these T cells have been further demonstrated to protect against malaria as in Hansen *et al*, (5) because the NK-T cells are invariant and only recognize one dominant antigen (unlike conventional T cells, these T cells do not vary their TCR repertoire), those skilled in the art would deduce, based on the present teaching, that expanding these T cells by exposure to GPI would provide protection against malaria. Applicant directs attention to Figure 1 of the specification and asserts that these T cells have a valuable effect in preventing disease in mice, (6) *P. berghei* malaria infection of mice and rats is well recognized by weight of scientific opinion to model the most important features of human malarial pathogenesis and Applicant submits Schofield *et al*, Evens *et al*, Barnell and Lou *et al*, (7) the ability of GPI molecules to induce T cell mediated immunity in *P. berghei* infected mice, as shown in the instant application, can be extrapolated to treating relevant diseases in other animals, including human.

It is the Examiner's position that: (1) Claims 1, 18 recite administering a "GPI complex", and Applicant has amended claim 81 and its dependent claims to delete the limitation "derivatives or equivalents thereof", (2) de Souza *et al* is not of record in the instant rejection, (3) & (4) Hansen *et al* (2003) teach that NK-T cells are correlated with partial protection against cerebral malaria in a mouse model or delay in disease onset, but not in prevention of disease, and further teach in the last sentence of the reference "These considerations raise the possibility of reducing susceptibility to severe malarial disease in human populations by immunomodulation via a Th2-biased, CD1-restricted glycolipid vaccine," indicating that in 2003, years after the effective filing date of the instant application, that reducing disease susceptibility, *i.e.,* prevention, was a still just a possibility, (5) NK-T cells are capable of recognizing antigens other than GPI, and Figure 1 in the instant specification shows that CD1.1/1.2 knock-out mice showed a high rate of *P. berghei*-induced malaria, indicating correlation, but not causation, (6) Schofield *et al*, Evens *et al*, Barnell and Lou *et al* do not teach prevention of malaria using a GPI, (7) the instant application does not disclose the ability of purified GPI molecules to induce T cell mediated immunity in *P. berghei* infected mice, nor does the instant specification disclose administering purified GPI molecules to treat or prevent malaria or any other disease or condition.

6. For the purpose of prior art rejections, the filing date of the instant claims 1-3, 9-16, 18, 81-88, 100, 102-106, 108-110, 116-120, 124 and 125 is deemed to be the filing date of the PCT application PCT/AU99/00929, *i.e.,* 10/27/99, as the foreign priority application AU PP 6758 does not support the claimed limitations of the instant application. There is no disclosure of the chemical species recited in the said instant claims in the said foreign priority application.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following grounds of rejection remain.

8. Claims 1-3, 9-16, 18, 81-88, 100 and 102 stand rejected under 35 U.S.C. 102(b) as being anticipated by Schofield *et al* (J. Exp. Med. 1/93 177: 145-153, of record) as evidenced by Nagata *et al* (Eur. J. Immunol. 1993 23: 1193-1196, of record), Gerold *et al* (Mol. Biochem. Parasit. 1996 75: 131-143, of record), Gerold *et al* (J. Biol. Chem. 1994 269(4): 2597-2606, of record), Berhe *et al* (Mol. Biochem. Parasit. 1999 103: 273-278, of record), Schofield *et al* (Science 283: 225-229, 1/8/99, of record), Joyce *et al* (Science 1998 279: 1541-1543, IDS reference) and Sieling *et al* (Science 1995 269: 227-230, IDS reference).

Schofield *et al* teach a strong correlation between TNF and IL-1 levels in sera of malarious individuals and the severity of the disease, wherein plasma TNF levels were twice as high in surviving cerebral malaria patients as in those with uncomplicated malaria, and those that died of the cerebral malarial disease had ten times elevated levels. Schofield *et al* teach that administration *in vivo* of specific neutralizing antibodies against TNF affords some protection to mice infected with lethal malaria. Schofield *et al* teach that excess production of TNF in response to the malarial parasite contributes to the severe pathology and death in both rodent and human infections. Schofield *et al* teach administration *in vivo* in mice of P. *falciparum* or T. *brucei* GPI or analogues that also comprise diacylglycerol and phosphatidylcholine. Schofield *et al* teach that several major antigens of the malaria parasite are covalently linked to GPI, including the MSP-1 and MSP-2 antigens on the merozoite surface, currently under consideration as vaccine candidates. Schofield *et al* teach that immunization of mice with highly purified malaria GPI prepared from mature P. *falciparum* MSP-2 leads to a serological anti-GPI

response with T independent features, and the anti-GPI sera are able even at high titration to neutralize TNF induction and lipogenesis by both the heterologous MSP-1 antigen and whole parasite extracts, *i.e.,* anti-GPI administered for treatment of induced malarial disease *in vivo* in mice. Schofield *et al* teach providing clinical protection against malarial disease, either by passive transfer of neutralizing anti-GPI antibodies or by immunization against the GPI or various non-toxic analogues for *in vivo* production of anti-GPI antibodies (especially page 152, page 149, page 150). Schofield *et al* teach cerebral malaria is a type of malaria to be treated by administering GPI (see entire article, especially introduction on pages 145-146, page 146 at the third full paragraph, results and discussion, page 152 at column 2).
Evidentiary reference Nagata *et al* teach that Th2 cells secrete IL-4, IL-5 and IL-6 and provide the major help for antibody production of T cells (especially first paragraph on page 1193).

Evidentiary reference Gerold *et al* (1996) teach that the MSP-1 and MSP-2 merozoite surface proteins of *Plasmodium falciparum* isolate FCBR are anchored via GPI to the membrane, the GPI anchors having the Mα2Mα2Mα6Mα4-GlcInositol phosphate linked to diacyl glycerol, a lipid. Gerold *et al* (1996) also teach that the core glycans of both protein-GPI anchors possess the same structure as the potential GPI-anchor precursor $Pf_{g1}\alpha$ taught by the evidentiary reference Gerold *et al* (1994) cited below (see entire article).

Evidentiary reference Gerold *et al* (1994) teach that the MSP-1 and MSP-2 merozoite surface proteins of *Plasmodium falciparum* isolate FCBR are anchored via GPI to the membrane. Gerold *et al* (1994) teach that MSP-1 and MSP-2 possess GPI anchors with the same neutral glycan as $Pf_{g1}\alpha$. Gerold *et al* (1994) teach that they are supposed to have the structure ethanolamine-phosphate-Mα2Mα2Mα6Mα4GlcN-PI based upon identical fragmentation products to the *T. brucei* GPI-anchor precursor P2, and the said structure further comprises a lipid (see entire article).

Evidentiary reference Berhe *et al* teach GPIs from different isolates of *Plasmodium falciparum,* including the isolate taught by the art reference Schofeld *et al* (1993), have a set of GPIs structurally identical to the GPIs described for the reference parasite line FCBR, and the core structure is ethanolamine-phosphate-Mα2Mα2Mα6Mα4-glucosamine-acyl-phosphatidylinositol or ethanolamine-phosphate-Mα2Mα6Mα4-glucosamine-acyl-phosphatidylinositol, and wherein the GPIs have ester linked fatty acids at the C-terminal end (see entire article).

Evidentiary reference Schofield *et al* (1999) teach that the GPI anchors in *Plasmodium falciparum* comprise the structure ethanolamine-phosphate-Mα2Mα2Mα6Mα4-GlcNα6-myoinositol phosphate-diacyl glycerol (see entire reference, especially Figure 1A). Schofield *et al* (1999) further teach that the proliferative and IL-4 (*i.e.,* Th2 cytokine) response to PfGPI of NK 1.1+/CD4+ T cells is independent of MHC and can be blocked by an anti-CD1 mAb, indicating CD1 restriction.

Evidentiary reference Joyce *et al* teach that CD1d binds GPI through its phosphatidylinositol aspect with high affinity. Joyce *et al* further teach that CD1d controls the function of NK1+ T cells that play an immunoregulatory role in responses to foreign and self antigens.

Evidentiary reference Sieling *et al* teach GPI-CD1-mediated stimulation of T cell subsets, the GPI from mycobacterial species possessing a phosphatidylinositol aspect similar to the GPI taught by the other evidentiary references cited herein.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. When a claim recites using an old composition or structure (*e.g.,* GPI or analogues) and the use is directed to a result or property of that composition or structure (activating $CD4^+$ $NK1.1^+$ Th2 cells following administration of GPI) then the claim is anticipated. See MPEP 2112.02. Also, see Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc. 58 USPQ2d 1508 (CA FC 2001); Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. v. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. v IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

Applicant's arguments in the amendment filed 5/18/07 have been fully considered, but are not persuasive.

Applicant's position is of record on pages 19-20, briefly that: the Schofield *et al* reference teaches that the administration of the GPI molecules caused the death of the host by activating macrophages that produce TNF.

It is the Examiner's position that the Schofield *et al* reference teaches administration of GPI by itself, said administration not resulting in death of the animals, said teaching meeting the instant claim limitations as enunciated supra. A subsequent experiment involving pre-administration of D-galactosamine followed by GPI resulted in death of a portion of the mice.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-3, 9-16, 18, 81-88, 100, 102-106, 108-110, 116-120, 124 and 125 stand rejected under 35 U.S.C. 103(a) as being obvious over WO 99/52547 (10/21/99, of record) in view of Gerold *et al* (J. Biol. Chem. 1994 269(4): 2597-2606, of record) and Gerold *et al* (Mol. Biochem. Parasit. 1996 75: 131-143, of record).

WO 99/52547 teaches treatment of malaria or other parasitic infections comprising administering CD1-binding GPI to induce a $CD4^+$ T cell response, including inducing B cell activation through a T cell response, *i.e.,* activation of $CD4^+$ Th2 cells (especially page 3 at lines 9-21, pages 9-10, 12, 18, 19 and claims). WO 99/52547 teaches *Plasmodium* genus and species (especially pages 3, 10, 11 and 12 and claims). WO 99/52547 further teaches phospholipids such as phosphatidylinositol, phosphatidylethanolamine and phosphatidylglycerol (page 21). WO 99/52547 teaches that the immunogenic composition for treating malaria can comprise a CD1-restricted lipid antigen from *Plasmodium*, such as a GPI (especially page 11 and claims).

WO 99/52547 does not teach the treatment of malaria or other parasitic infections comprising a GPI that comprises the structure recited in the instant claims.

Gerold *et al* (1994) teach that the MSP-1 and MSP-2 merozoite surface proteins of *Plasmodium falciparum* isolate FCBR are anchored via GPI to the membrane. Gerold *et al* (1994) teach that MSP-1 and MSP-2 possess GPI anchors with the same neutral glycan as $Pf_{g1}\alpha$. Gerold *et al* (1994) teach that they are supposed to have the structure ethanolamine-phosphate-Mα2Mα2Mα6Mα4GlcN-PI based upon identical fragmentation products to the *T. brucei* GPI-anchor precursor P2, and the said structure further comprises a lipid (see entire article). Gerold *et al* (1994) teach that elucidation of the structures of malarial GPIs may provide a basis for the development of a glycolipid-based vaccine for malaria (page 2605, column 2, second to last paragraph).

Gerold *et al* (1996) teach that the MSP-1 and MSP-2 merozoite surface proteins of *Plasmodium falciparum* isolate FCBR are anchored via GPI to the membrane, the GPI anchors having the Mα2Mα2Mα6Mα4-GlcInositol phosphate linked to diacyl glycerol, a lipid. Gerold *et al* (1996) also teach that the core glycans of both protein-GPI anchors possess the same structure as the potential GPI-anchor precursor $Pf_{g1}\alpha$ taught by the Gerold *et al* (1994) cited below. Gerold *et al* (1996) teach that antibodies to malarial GPIs are able to block cytokine induction by whole parasite extracts, that the said GPIs are the major toxin of malarial origin and that they play a central role in the etiology of clinical severe and cerebral malaria (see entire article).
It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the malarial GPI taught by either Gerold *et al* reference as the GPI taught by WO 99/52547 in the method taught by WO 99/52547.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat malaria because WO 99/52547 teaches treating malaria by administering CD1-binding GPI to induce a $CD4^+$ T cell response, and the Gerold *et al* references teach the structure of the MSP-1 and MSP-2 GPIs from malaria that are taught by the said references to provide a basis for vaccines and that play a central role in the etiology of clinical severe and cerebral malaria.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. When a claim recites using an old composition or structure (*e.g.,* GPI or analogues) and the use is directed to a result or property of that composition or structure (activating $CD4^+$ $NK1.1^+$ Th2 cells following administration of GPI) then the claim is anticipated. See MPEP 2112.02. Also, see Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc. 58 USPQ2d 1508 (CA FC 2001); Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. v. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. v IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

Applicant's arguments of record in the amendment filed 5/18/07 on pages 21-22 have been fully considered, but are not persuasive.

It is the Examiner's position that: (1) The Examiner withdrew the previous anticipation rejection based upon WO 99/52547 because Applicant amended the claims; (2) the said WO reference has a publication date of October 21, 1999, well before Applicant's priority date for art, *i.e.,* 10/27/99, as Applicant's foreign priority document does not disclose any of the GPI species recited in the instant claims, as enunciated supra; (3) the secondary references teach the structure of theMSP-1 and MSP-2 GPI's from malaria that is recited in the instant claims.

11. Claims 1-3, 9-16, 18, 81-88, 100, 102-106, 108-110, 116-120, 124 and 125 stand rejected under 35 U.S.C. 103(a) as being obvious over WO 99/52547 (10/21/99, of record) in view of Schofield *et al* (J. Exp. Med. 1/93 177: 145-153, of record).

WO 99/52547 teaches treatment of malaria or other parasitic infections comprising administering CD1-binding GPI to induce a $CD4^+$ T cell response, including also inducing B cell activation through a T cell response, *i.e.,* activation of $CD4^+$ Th2 cells (especially page 3 at lines 9-21, pages 9-10, 12, 18, 19 and claims). WO 99/52547 teaches *Plasmodium* genus and species (especially pages 3, 10, 11 and 12 and claims). WO 99/52547 further teaches phospholipids such as phosphatidylinositol, phosphatidylethanolamine and phosphatidylglycerol (page 21). WO 99/52547 teaches that the immunogenic composition for treating malaria can comprise a CD1-restricted lipid antigen from *Plasmodium*, such as a GPI (especially page 11 and claims).

WO 99/52547 does not teach the treatment of malaria or other parasitic infections comprising a GPI that comprises the structure recited in the instant claims.

Schofield *et al* teach a strong correlation between TNF and IL-1 levels in sera of malarious individuals and the severity of the disease, wherein plasma TNF levels were twice as high in surviving cerebral malaria patients as in those with uncomplicated malaria, and those that died of the cerebral malarial disease had ten times elevated levels. Schofield *et al* teach that administration *in vivo* of specific neutralizing antibodies against TNF affords some protection to mice infected with lethal malaria. Schofield *et al* teach that excess production of TNF in response to the malarial parasite contributes to the severe pathology and death in both rodent and human infections. Schofield *et al* teach administration *in vivo* in mice of P. *falciparum* or T. *brucei* GPI or analogues that also comprise diacylglycerol and phosphatidylcholine. Schofield *et al* teach that several major antigens of the malaria parasite are covalently linked to GPI, including the MSP-1 and MSP-2 antigens on the merozoite surface, currently under consideration as vaccine candidates. Schofield *et al* teach that immunization of mice with highly purified malaria GPI prepared from mature P. *falciparum* MSP-2 leads to a serological anti-GPI response with T independent features, and the anti-GPI sera are able even at high titration to neutralize TNF induction and lipogenesis by both the heterologous MSP-1 antigen and whole parasite extracts, *i.e.,* anti-GPI administered for treatment of induced malarial disease *in vivo* in mice. Schofield *et al* teach providing clinical protection against malarial disease, either by passive transfer of neutralizing anti-GPI antibodies or by immunization against the GPI or various non-toxic analogues for *in vivo* production of anti-GPI antibodies (especially page 152, page 149, page 150). Schofield *et al* teach cerebral malaria is a type of malaria to be treated by administering GPI (see entire article, especially introduction on pages 145-146, page 146 at the third full paragraph, results and discussion, page 152 at column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the P. *falciparum* GPI taught by Schofield *et al* as the GPI in the method taught by WO 99/52547.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat malaria because WO 99/52547 teaches treating malaria by administering CD1-binding GPI to induce a $CD4^+$ T cell response, and Schofield *et al* teach the structure of a P. *falciparum* GPI that is linked to the MSP-1 and MSP-2 antigens on the malarial merozoite surface that are under consideration as vaccine candidates, that immunization of mice with highly purified malaria GPI prepared from mature P. *falciparum* MSP-2 leads to a serological anti-GPI response with T independent features, and that the anti-GPI sera are able even at high titration to neutralize TNF induction and lipogenesis by both the heterologous MSP-1 antigen and whole parasite extracts.

Applicant's arguments of record in the amendment filed 5/18/07 on pages 22-23 have been fully considered, but are not persuasive.

It is the Examiner's position that: (1) The Examiner withdrew the previous anticipation rejection based upon WO 99/52547 because Applicant amended the claims; (2) the said WO reference has a publication date of October 21, 1999, before Applicant's priority date for art, *i.e.,* 10/27/99, as Applicant's foreign priority document does not disclose any of the GPI species recited in the instant claims, as enunciated supra; (3) the secondary reference teaches malarial GPI MSP-2 that has the structure recited in the instant claims.

12. Claims 1-3, 9-16, 18, 81-88, 100, 102-106, 108-110, 116-120, 124 and 125 stand rejected under 35 U.S.C. 103(a) as being obvious over WO 99/12562 A1 (3/18/99, of record) in view of Gerold *et al* (J. Biol. Chem. 1994 269(4): 2597-2606, of record) and Gerold *et al* (Mol. Biochem. Parasit. 1996 75: 131-143, of record).

WO 99/12562 A1 teaches treatment parasitic infections in a mammal, including malaria, comprising administering a CD1-restricted antigen such as a GPI that comprises a hydrophilic component conjugated to a hydrophobic component that comprises one or more saturated or unsaturated acyl chains and wherein one or more of the acyl chains is bonded to a phosphate group. WO 99/12562 A1 teaches that glycosyl phosphatidylinositols (GPIs) have two alkyl chains and a hydrophilic head group that conform to the CD1d motif and are presented by CD1d in both humans and mice (especially abstract, page 3 at lines 8-15, page 16 at lines 25-30, page 28 at lines 15-33, page 29 at lines1-10, claims 10-17).

WO 99/12562 A1 does not teach the treatment of malaria or other parasitic infections comprising a GPI that comprises the structure recited in the instant claims.

Gerold *et al* (1994) teach that the MSP-1 and MSP-2 merozoite surface proteins of *Plasmodium falciparum* isolate FCBR are anchored via GPI to the membrane. Gerold *et al* (1994) teach that MSP-1 and MSP-2 possess GPI anchors with the same neutral glycan as $Pf_{g1}\alpha$. Gerold *et al* (1994) teach that they are supposed to have the structure ethanolamine-phosphate-Mα2Mα2Mα6Mα4GlcN-PI based upon identical fragmentation products to the *T. brucei* GPI-anchor precursor P2, and the said structure further comprises a lipid (see entire article). Gerold *et al* (1994) teach that elucidation of the structures of malarial GPIs may provide a basis for the development of a glycolipid-based vaccine for malaria (page 2605, column 2, second to last paragraph).

Gerold *et al* (1996) teach that the MSP-1 and MSP-2 merozoite surface proteins of *Plasmodium falciparum* isolate FCBR are anchored via GPI to the membrane, the GPI anchors having the Mα2Mα2Mα6Mα4-GlcInositol phosphate linked to diacyl glycerol, a lipid. Gerold *et al* (1996) also teach that the core glycans of both protein-GPI anchors possess the same structure as the potential GPI-anchor precursor $Pf_{g1}\alpha$ taught by the

Gerold *et al* (1994) cited below. Gerold *et al* (1996) teach that antibodies to malarial GPIs are able to block cytokine induction by whole parasite extracts, that the said GPIs are the major toxin of malarial origin and that they play a central role in the etiology of clinical severe and cerebral malaria (see entire article).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the malarial GPI taught by either Gerold *et al* reference as the GPI taught by WO 99/12562 A1 in the method taught by WO 99/12562 A1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat malaria because WO 99/12562 A1 teaches treating malaria by administering CD1-binding GPI to induce a T cell response and treat malaria, and the Gerold *et al* references teach the structure of the MSP-1 and MSP-2 GPIs from malaria that are taught by the said references to provide a basis for vaccines and that play a central role in the etiology of clinical severe and cerebral malaria.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. When a claim recites using an old composition or structure (*e.g.,* GPI or analogues) and the use is directed to a result or property of that composition or structure (activating $CD4^+$ $NK1.1^+$ Th2 cells following administration of GPI) then the claim is anticipated. See MPEP 2112.02. Also, see Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc. 58 USPQ2d 1508 (CA FC 2001); Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. v. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. v IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

Applicant's arguments of record in the amendment filed 5/18/07 on pages 12-24 have been fully considered, but are not persuasive.

It is the Examiner's position that: (1) the WO 99/12562 A1 reference has a publication date of March 18, 1999, well before Applicant's priority date for art, *i.e.,* 10/27/99, as Applicant's foreign priority document does not disclose any of the GPI species recited in the instant claims, as enunciated supra; (3) the secondary reference teaches teach the structure of the MSP-1 and MSP-2 malarial GPI that have the structure recited in the instant claims.

13. Claims 1-3, 9-16, 18, 81-88, 100, 102-106, 108-110, 116-120, 124 and 125 stand rejected under 35 U.S.C. 103(a) as being obvious over WO 99/12562 A1 (3/18/99, of record) in view of Schofield *et al* (J. Exp. Med. 1/93 177: 145-153, of record).

WO 99/12562 A1 teaches treatment parasitic infections in a mammal, including malaria, comprising administering a CD1-restricted antigen such as a GPI that comprises a hydrophilic component conjugated to a hydrophobic component that comprises one or more saturated or unsaturated acyl chains and wherein one or more of the acyl chains is bonded to a phosphate group. WO 99/12562 A1 teaches that glycosyl phosphatidylinositols (GPIs) have two alkyl chains and a hydrophilic head group that conform to the CD1d motif and are presented by CD1d in both humans and mice (especially abstract, page 3 at lines 8-15, page 16 at lines 25-30, page 28 at lines 15-33, page 29 at lines1-10, claims 10-17).

WO 99/12562 A1 does not teach the treatment of malaria or other parasitic infections comprising a GPI that comprises the structure recited in the instant claims.

Schofield *et al* teach a strong correlation between TNF and IL-1 levels in sera of malarious individuals and the severity of the disease, wherein plasma TNF levels were twice as high in surviving cerebral malaria patients as in those with uncomplicated malaria, and those that died of the cerebral malarial disease had ten times elevated levels. Schofield *et al* teach that administration *in vivo* of specific neutralizing antibodies against TNF affords some protection to mice infected with lethal malaria. Schofield *et al* teach that excess production of TNF in response to the malarial parasite contributes to the severe pathology and death in both rodent and human infections. Schofield *et al* teach administration *in vivo* in mice of P. *falciparum* or T. *brucei* GPI or analogues that also comprise diacylglycerol and phosphatidylcholine. Schofield *et al* teach that several major antigens of the malaria parasite are covalently linked to GPI, including the MSP-1 and MSP-2 antigens on the merozoite surface, currently under consideration as vaccine candidates. Schofield *et al* teach that immunization of mice with highly purified malaria GPI prepared from mature P. *falciparum* MSP-2 leads to a serological anti-GPI response with T independent features, and the anti-GPI sera are able even at high titration to neutralize TNF induction and lipogenesis by both the heterologous MSP-1 antigen and whole parasite extracts, *i.e.,* anti-GPI administered for treatment of induced malarial disease *in vivo* in mice. Schofield *et al* teach providing clinical protection against malarial disease, either by passive transfer of neutralizing anti-GPI antibodies or by immunization against the GPI or various non-toxic analogues for *in vivo* production of anti-GPI antibodies (especially page 152, page 149, page 150). Schofield *et al* teach cerebral malaria is a type of malaria to be treated by administering GPI (see entire article, especially introduction on pages 145-146, page 146 at the third full paragraph, results and discussion, page 152 at column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the P. *falciparum* GPI taught by Schofield *et al* as the GPI in the method taught by WO 99/12562 A1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat malaria because WO 99/12562 A1 teaches treating malaria by administering CD1-binding GPI to induce a T cell response, and Schofield *et al* teach the structure of a P. *falciparum* GPI that is linked to the MSP-1 and MSP-2 antigens on the malarial merozoite surface that are under consideration as vaccine candidates, that immunization of mice with highly purified malaria GPI prepared from mature P. *falciparum* MSP-2 leads to a serological anti-GPI response with T independent features, and that the anti-GPI sera are able even at high titration to neutralize TNF induction and lipogenesis by both the heterologous MSP-1 antigen and whole parasite extracts.

Applicant's arguments of record in the amendment filed 5/18/07 on pages 12-24 have been fully considered, but are not persuasive.

It is the Examiner's position that: (1) the WO 99/12562 A1 reference has a publication date of March 18, 1999, well before Applicant's priority date for art, *i.e.,* 10/27/99, as Applicant's foreign priority document does not disclose any of the GPI species recited in the instant claims, as enunciated supra; (3) the secondary reference teaches teach the MSP-1 and MSP-2 malarial GPI that have the structure recited in the instant claims.

The following is a new ground of rejection necessitated by Applicant's IDS filed 6/11/07.

14. Claims 1-3, 9-12, 14-16, 18, 81-87, 100 and 102 are rejected under 35 U.S.C. 103(a) as being obvious over WO 96/34105 A1 (IDS reference submitted 6/11/07) as evidenced by Gerold *et al* (Mol. Biochem. Parasit. 1996 75: 131-143, of record), Gerold *et al* (J. Biol. Chem. 1994 269(4): 2597-2606, of record) and Joyce *et al* (Science 1998 279: 1541-1543, IDS reference).

WO 96/34105 A1 teaches producing antibodies (*i.e.,* activating Th cell help for antibody production) by administering a complex of GPI-antigen, the antigen such as a parasite polypeptide, in particular, a *P. falciparum* polypeptide (see entire reference, especially abstract, page 3 at lines 4-15, page 12, page 13 at lines 1-15, claims).

WO 96/34105 A1 does not teach the structure of the GPI used in the method.

Gerold *et al* (1996) teach that the MSP-1 and MSP-2 merozoite surface proteins of *Plasmodium falciparum* isolate FCBR are anchored via GPI to the membrane, the GPI anchors having the Mα2Mα2Mα6Mα4-GlcInositol phosphate linked to diacyl glycerol, a lipid. Gerold *et al* (1996) also teach that the core glycans of both protein-GPI anchors

possess the same structure as the potential GPI-anchor precursor $Pf_{g1}\alpha$ taught by the evidentiary reference Gerold *et al* (1994) cited below (see entire article).

Gerold *et al* (1994) teach that the MSP-1 and MSP-2 merozoite surface proteins of *Plasmodium falciparum* isolate FCBR are anchored via GPI to the membrane. Gerold *et al* (1994) teach that MSP-1 and MSP-2 possess GPI anchors with the same neutral glycan as $Pf_{g1}\alpha$. Gerold *et al* (1994) teach that they are supposed to have the structure ethanolamine-phosphate-Mα2Mα2Mα6Mα4GlcN-PI based upon identical fragmentation products to the *T. brucei* GPI-anchor precursor P2, and the said structure further comprises a lipid (see entire article).

Joyce *et al* teach that CD1d binds GPI through its phosphatidylinositol aspect with high affinity. Joyce *et al* further teach that CD1d controls the function of NK1+ T cells that play an immunoregulatory role in responses to foreign and self antigens.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the GPI from *P. falciparum* taught by Gerold *et al* (1996) and Gerold *et al* (1994), that is taught by Joyce *et al* to bind CD1d, as the GPI in the complex comprising GPI and a *P. falciparum* polypeptide antigen taught by WO 96/34105 A1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because WO 96/34105 A1 teaches a GPI-peptide complex for immunizing animals and producing antibodies wherein the peptide is from *P. falciparum*, Gerold *et al* (1996) and Gerold *et al* (1994) teach the structure of GPI from *P. falciparum*, and Joyce et al teach that CD1d binds GPI through its phosphatidylinositol aspect with high affinity. Joyce *et al* further teach that CD1d controls the function of NK1+ T cells that play an immunoregulatory role in responses to foreign and self antigens.

Claims 16 and 83 are included in this rejection because it is an expected property of the NK1+ T cells taught by Joyce *et al* that they are CD4+ T cells.

Claims 81-87 are included in this rejection because GPI is administered even though it is present in a complex.

Claim 102 is included in this rejection because it is an expected property of the art method that the activated T cells induce or up-regulate a TH2 type response.

15. The Declaration of Louis Schofield and Diana Hansen under 35 USC 1.132 filed 5/18/07 has overcome the prior art rejections of record based upon Schofield *et al* (Science 283: 225-229, 1/6/99).

16. No claim is allowed.

17. The references WO 99/52547 and Schofield *et al* (1993) have been crossed-out by the Examiner on Applicant's Form 1449 filed 6/11/07 because they have been cited previously by the Examiner.

18. Applicant's amendment necessitated new grounds of rejection presented in this Office action. In addition, Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 6/11/07 prompted a new ground of rejection presented in this Office action.

Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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